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September 1956

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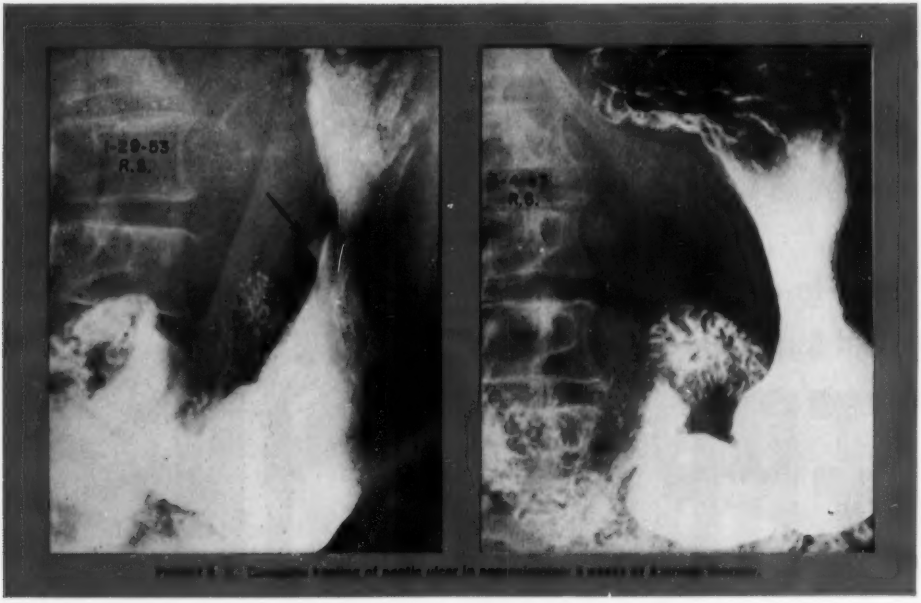

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EFFECTS OF TRICYCLAMOL ON GASTRIC SECRETION AND GASTROINTESTINAL MOTILITY IN PEPTIC ULCER: EXPERIMENTAL STUDIES AND CLINICAL OBSERVATIONS
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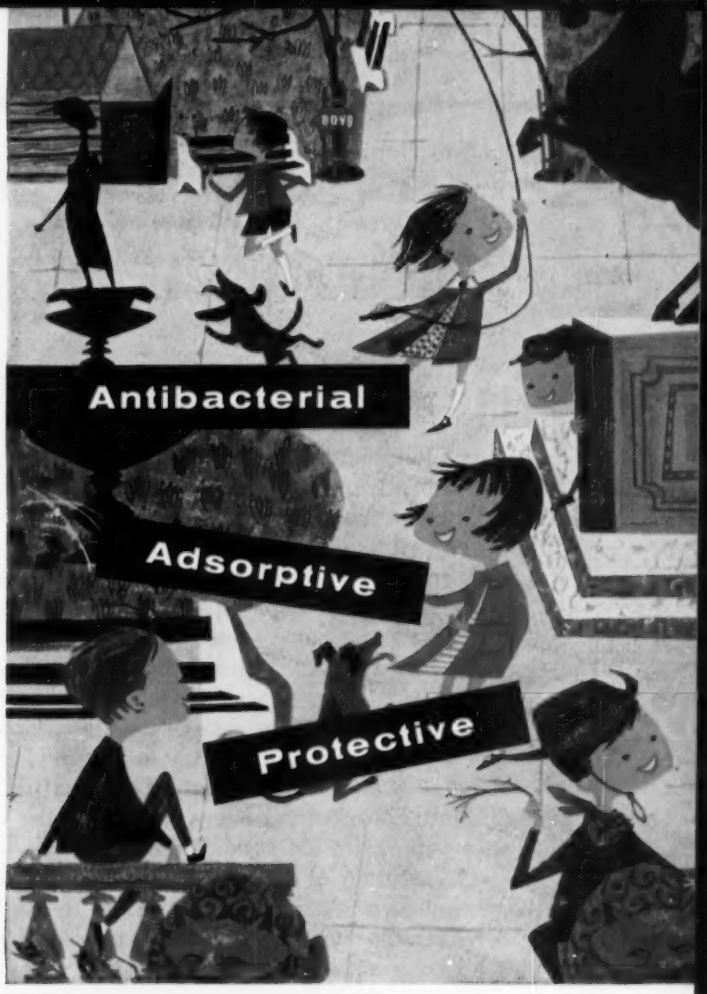

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2. Gray, Horace, and Tainter, M. L.: *Am. Jour. Digest. Dis.*, 8:130, Apr., 1941.

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Effects of Tricyclamol On Gastric Secretion and Gastrointestinal Motility In Peptic Ulcer

Experimental Studies and Clinical Observations

ANTHONY M. KASICH, M.D., AUSTIN P. BOLEMAN, JR., M.D., and JEANNE C. RAFSKY, M.D.

THERE IS NO AGREEMENT among investigators regarding the specific factors which produce symptoms in peptic ulcer. Two factors, however, appear to be present with sufficient frequency to indicate that they may account for pain and disturbed gastrointestinal function in patients with peptic ulcer. These factors are an increased production of gastric secretion and of hydrochloric acid, and an increase in activity of the smooth muscles of the stomach and intestines. Numerous anticholinergic agents have been utilized in an attempt to restore physiologic equilibrium to the secretory and motor function of the gastrointestinal tract. Some of these agents have been beneficial but the search for better agents with specific antisecretory and antispasmodic actions and without widespread parasympathetic response continues. The recent introduction of so many drugs of this character shows that the ideal agent has not yet been produced.

From the Lenox Hill Hospital, New York, N. Y.

These studies were supported and tricyclamol supplied by Burroughs Wellcome & Co. (U.S.A.), Inc.

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PHARMACOLOGY

Recently, a new anticholinergic, tricyclamol,* has been synthesized. Chemically, this compound is 1-cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methchloride. Following initial laboratory studies,[1] which suggested the drug's ability to reduce both secretory and motor function of the stomach, detailed pharmacologic investigations of tricyclamol were carried out by Lee and his associates.[2] In pylorus-ligated rats they demonstrated a marked decrease in volume of gastric secretion and hydrochloric acid production following the administration of tricyclamol. The drug was also effective in inhibiting motility in isolated intestinal segments stimulated with methacholine. Similar effects were observed in dogs with Thiry fistulas of the jejunum and ileum. In common with other cholinergic blocking agents, tricyclamol appeared more effective when given parenterally than by mouth. Very high dosage of the drug blocked synaptic conduction in sympathetic ganglia; near-lethal dosage interfered with myoneural conduction in a curare-like manner. The high potency and low toxicity of this agent has suggested to us its possible value in the treatment of peptic ulcer. This study was undertaken to determine the antisecretory and antispasmodic effects of tricyclamol on the stomach and duodenum, and to evaluate further its usefulness in treatment of peptic ulcer.

EXPERIMENTAL STUDIES

Methods

Fasting Gastric Secretions

The effect of tricyclamol on the acidity of fasting gastric secretion was studied in 9 patients with duodenal ulcer and 1 with gastric ulcer. Following a 12-hour fast, a Levin tube was passed into the stomach. Any gastric residue was aspirated and discarded. Four specimens of gastric secretion were withdrawn at 15-minute intervals and titrated for acidity. A suspension of 100 mg. tricyclamol was then administered to the patient by means of the Levin tube. Forty-five minutes later 4 additional specimens were collected at 15-minute intervals and again titrated for acidity (Fig. 1).

Alcohol-Stimulated Gastric Secretion

The effect of tricyclamol was studied in 6 patients following alcohol stimulation of gastric secretion. After complete aspiration of the

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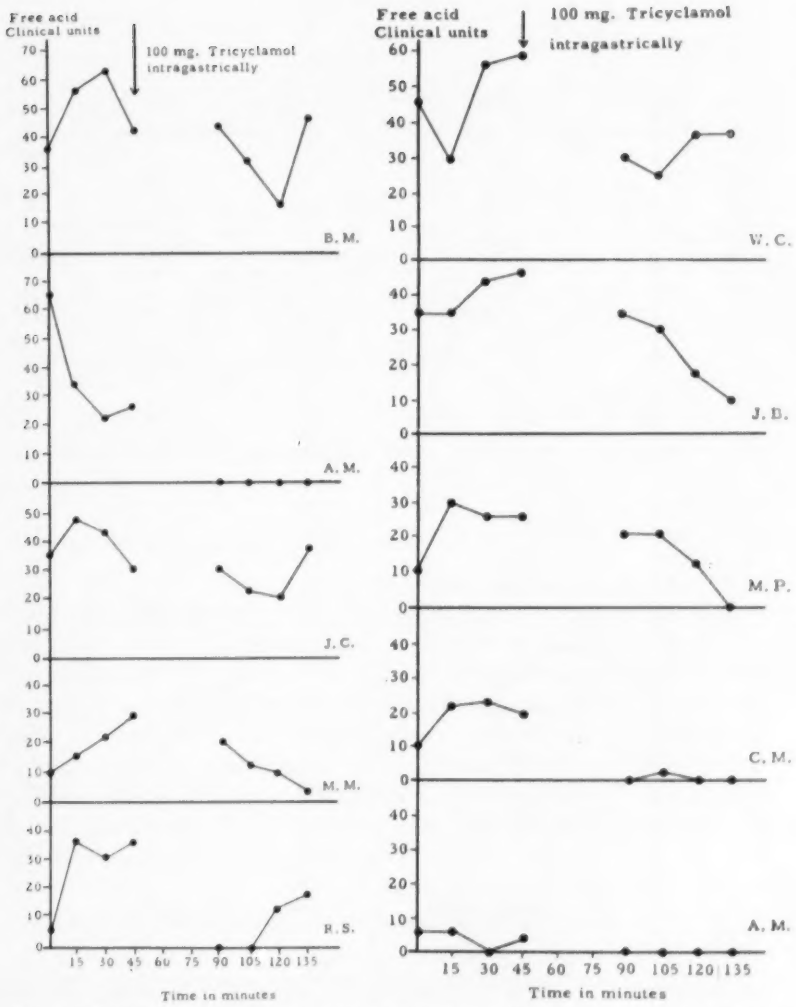


Fig. 1. **Effect of tricyclamol on acidity of basal secretion. A.M. has gastric ulcer; all others duodenal ulcer.**

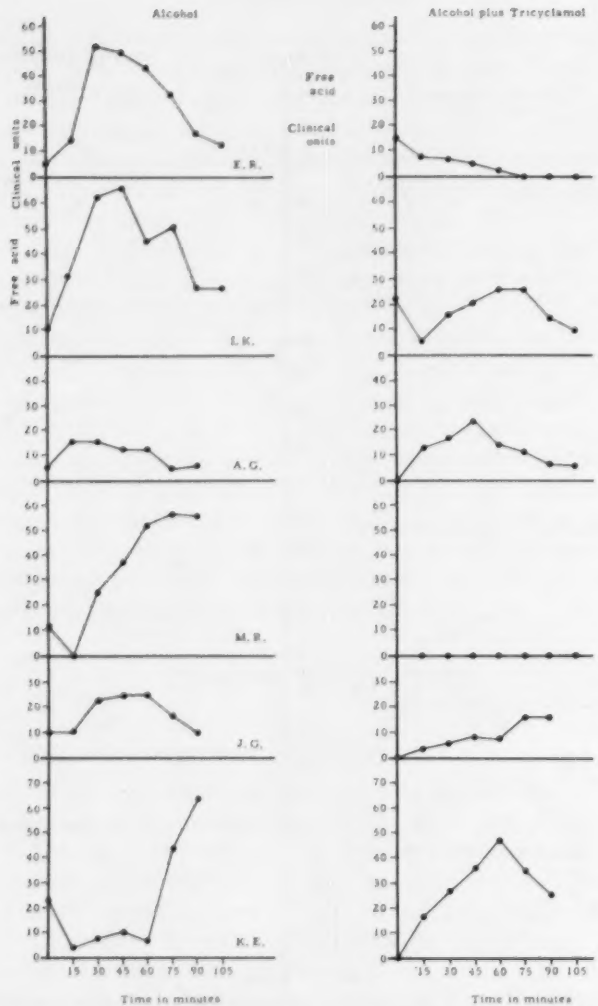


Fig. 2. **Effect of tricyclamol on acidity of alcohol-stimulated secretion.**

fasting stomach, 200 cc. of 5% alcohol was administered by means of the Levin tube. Specimens were aspirated every 15 minutes for 90 minutes. On another day a suspension containing 100 mg. of tricyclamol was injected through the tube into the stomach and 45 minutes later 200 cc. of 5% alcohol was placed in the stomach. At 15-minute

TABLE 1. Effect of Tricyclamol on Secretion in Response to Insulin Hypoglycemia

Patient	After insulin[a]					After insulin[a] plus 100 mg. tricyclamol				
	Fasting	30′	60′	90′	120′	Fasting	30′	60′	90′	120′
HH	32	18	84	86	80	5	50	36	76	64
LP	8	8	48	44	36	20	45	46	118	74
JL	0	10	90	75	0	0	10	..	90	85
JG	32	54	..	37	22	20	24	26	40	76
TY	8	20	18	20	32	12	14	6	70	58
MC	..	46	..	78	98	0	36	60	104	102
JB	66	36	118	120	132	40	50	70	76	80
NZ	50	48	58	110	106	0	4	4	0	0
HR	14	22	130	116	105	26	0	130	114	88
ES	52	48	76	100	24	46	44	70	88	72

All figures represent clinical units of hydrochloric acid.
[a] 15 units intravenously.

intervals samples of gastric juice were withdrawn and titrated for acidity (Fig. 2).

Insulin-Stimulated Gastric Secretion

The effect of tricyclamol on insulin-stimulated gastric secretion was determined in 10 patients. After titrating a fasting sample of gastric juice, 15 units of insulin was given intravenously. At 30-minute intervals additional samples of gastric contents were aspirated and titrated for acidity. On another day, 100 mg. tricyclamol was given orally to patients 45 minutes prior to an identical dose of insulin as previously given. Specimens were then withdrawn from the stomach at 30-minute intervals for 120 minutes. Determination of the acidity of each sample was made. In every case the glucose level reached 50 mg. or less per 100 cc. of blood (Table 1).

Motility of Stomach and Small Intestine

In 10 patients the effect of tricyclamol on the motility of the stomach and small intestine was determined by noting the progress of barium according to the methods of Chapman *et al.*[3] X-ray films were taken of the upper gastrointestinal tract 15, 30, and 60 minutes after the ingestion of barium (Fig. 3). On another day, barium was given 1 hour after 100 mg. of orally administered tricyclamol. X-ray films were then taken 15, 30, and 60 minutes later (see Fig. 4; and Table 2).

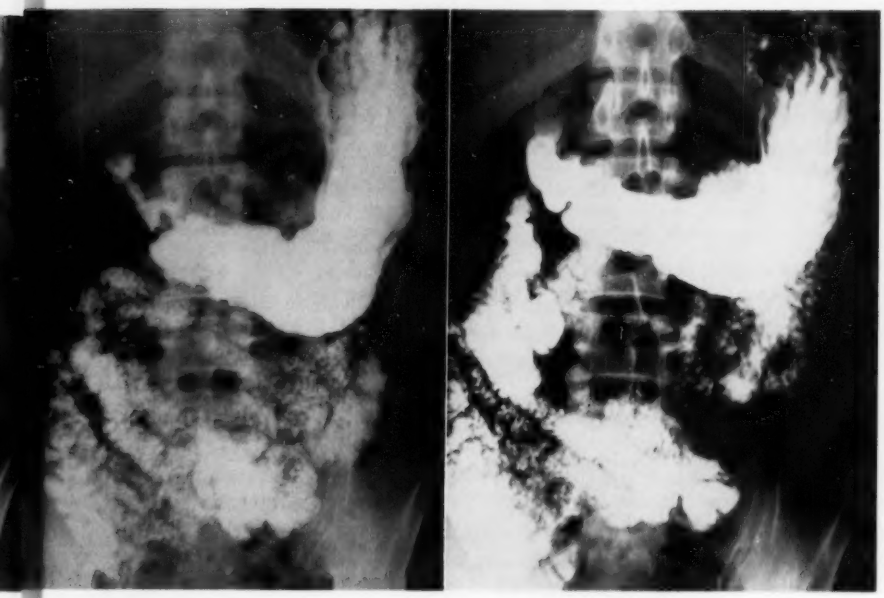
Fig. 3. **Progress of barium through the gastrointestinal tract in patient with duodenal ulcer. Barium administered at 9:00 a.m. Films taken at 9:15, 9:30, and 10:00 a.m.**

Results

Orally administered tricyclamol had a definite inhibitory action on the acidity of the fasting gastric juice. While there was a great variation in the response of the individual patient to 100 mg. of tricyclamol, the general pattern was one of diminution. In 3 patients achlorhydria lasting 2 hours (the duration of observation) was produced. Because of technical problems we did not measure the total amount of secretion. It was our impression, however, that in most cases the volume was decreased.

Tricyclamol, like other anticholinergic quaternary ammonium compounds, is more effective and consistent in action when given parenterally than orally. In 5 subjects who received 20 mg. of tricyclamol subcutaneously every 6 hours, Ruffin[4] found a decrease in the volume of secretion in every case, the average decrease being 58 per cent. The decrease in hydrochloric acid averaged 44 per cent.

In 6 patients, alcohol-stimulated secretion of hydrochloric acid was decreased by 100 mg. of tricyclamol orally. Two patients who secreted juice of high acidity in response to alcohol developed achlorhydria. In 1 case acid was absent for 2 hours, at which time the experiment was



terminated. The reasons for this reduction of acidity are not clear. It is possible that tricyclamol acts directly on the parietal cell, blocking the action of acetylcholine released by vagal fibers terminating within the cell.[5-8] The explanation for the failure of tricyclamol to diminish the acidity of secretion in response to insulin hypoglycemia is unknown.

The inhibitory effect of tricyclamol on the motility of the stomach and small intestine was demonstrated in 10 patients. In most patients with peptic ulcer, gastric peristalsis is very active and intestinal hypermotility is the rule. In 6 of 10 patients with peptic ulcer receiving no tricyclamol barium was usually found to have entered the ileum in 30 minutes and in 4 cases to have passed through the ileum in less than 1 hour. We have demonstrated that 100 mg. of tricyclamol orally causes a decrease in gastric peristalsis with retarded emptying and appreciably slows transit through the small intestine (Fig. 4).

CLINICAL OBSERVATIONS ON TRICYCLAMOL

Material and Method

Tricyclamol was given orally to 105 patients with peptic ulcer (Table 3). Hospitalized patients were placed on a modified Sippy

TABLE 2. Effect of 100 mg. Tricyclamol Orally on Intestinal Motility

Case	Medication	Estimated location of head of column of barium		
		15 min.	30 min.	60 min.
1	No drug	Upper jejunum	Upper ileum	Terminal ileum
	Tricyclamol	Second portion duodenum	Mid-jejunum	Mid-jejunum
2	No drug	At duodenal bulb	Beginning of ileum	Well into ileum
	Tricyclamol	Second portion duodenum	Mid-jejunum	Mid-jejunum
3	No drug	Upper jejunum	Beginning of ileum	Transverse colon
	Tricyclamol	Third portion duodenum	Mid-jejunum	Lower jejunum
4	No drug	Just beyond ligament of Treitz	Lower jejunum	Well into ileum
	Tricyclamol	Second portion duodenum	Upper jejunum	Mid-jejunum
5	No drug	At ligament of Treitz	Beginning of ielum	Ascending colon
	Tricyclamol	At duodenal bulb	Upper jejunum	Mid-jejunum
6	No drug	Well into jejunum	Upper ileum	Terminal ileum
	Tricyclamol	Upper jejunum	Mid-jejunum	Beginning of ileum
7	No drug	Upper jejunum	Upper ileum	Cecum
	Tricyclamol	Second portion duodenum	Upper jejunum	Lower jejunum
8	No drug	Just beyond ligament of Treitz	Lower jejunum	Lower ileum
	Tricyclamol	Second portion duodenum	Upper jejunum	Mid-jejunum
9	No drug	At ligament of Treitz	Well into jejunum	Lower ileum
	Tricyclamol	At duodenal bulb	Upper jejunum	Lower jejunum
10	No drug	Third portion duodenum	Lower jejunum	Ascending colon
	Tricyclamol	Second portion duodenum	Upper jejunum	Lower jejunum

regimen, with antacids and, when indicated, sedatives. Ambulatory patients were on convalescent ulcer diets. Alcohol, coffee, and smoking were interdicted. All patients received 50 mg. of tricyclamol 4 times a day. With this dosage maximal clinical improvement occurred and side reactions were seldom troublesome. The drug was given as a part of routine ulcer therapy and no stress was laid on the fact that a new agent was being used. Most of these patients had ulcers of long duration. Eighteen patients had ulcer symptoms for more than 20 years, 21 for more than 15 years, and 30 for more than 10 years. Twenty-four patients had symptoms for more than 5 years and only 12 had symptoms of less than 5 years' duration. Seventy-seven patients had been hospitalized either because of a complication or because of intractability. Thirty-three patients received tricyclamol for 12–20 months, 50 for 3–12 months, and 22 for from less than 1 month to 3 months.

Results of Treatment

Complete Symptomatic Relief

The results can be summarized as follows: in 76 patients, 16 of whom received tricyclamol for 12 or more months, the results were good and complete symptomatic relief was obtained. These patients have been maintained on tricyclamol 50 mg. 3 times a day and 50 mg. before retiring. Patients requiring any other medication for relief of symptoms are not included in this group. The only dietary restrictions have been the avoidance of coarse, fibrous, and spicy foods, and alcohol and coffee. Most of these patients abstained from smoking. None exhibited symptoms of recurrence during the period of observation and all were able to continue their usual occupation.

Fair Relief of Symptoms

In 21 patients the results were fair. In this group, patients obtained a large measure of symptomatic relief and many tolerated a liberal diet. In some cases the striking initial improvement was not sustained. While characteristic pain was absent, some patients complained of vague distress relieved by antacids and at times by sedatives. *It is worth noting that there was not always complete correlation between relief of symptoms and disappearance of the ulcer crater.* A few patients in whom the ulcer had healed still complained of distress, while others were free of symptoms in spite of persistence of craters. Two of these patients with marginal ulcer obtained relief of all symptoms of ulcer origin. They continued, however, to have some postprandial distress of the dumping type. The patient with duodenitis included in this group was relieved of his ulcer-like symptoms, but continued to complain of occasional heartburn (see Table 3).

No Relief and Discontinuance

Three patients treated less than 1 month obtained no relief with tricyclamol. One patient after a week's treatment refused the drug, claiming that he obtained more satisfactory results with tincture of belladonna. Two patients refused tricyclamol after 2 weeks' trial, one because of severe constipation and the other because it caused insufferable blurring of vision.

Failure and Complications

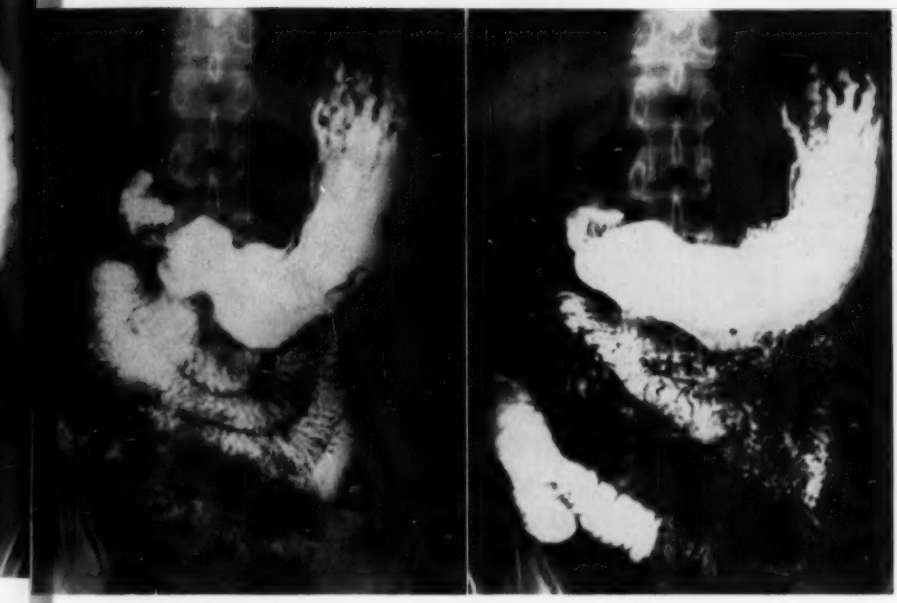
In 5 patients the results were poor. Two patients who were receiving adequate doses of tricyclamol and who were asymptomatic had

Fig. 4. **Same patient as in Fig. 3. Tricyclamol, 100 mg., was given at 8:00 a.m. One hour later the patient was given barium and films were taken at 9:15, 9:30, and 10:00 a.m. Note retardation of transit through the small intestine.**

hemorrhages. In 2 patients the craters became larger, and 1 patient was operated upon because of the failure of tricyclamol to relieve pain.

EVALUATION OF RESULTS

The difficulties in evaluating any new agent in treatment of a chronic disease such as peptic ulcer are obvious. First and foremost, uncomplicated peptic ulcer may heal spontaneously. Also, the disease is subject to remissions and exacerbations and a patient who is having so much stress that he is unable to work may with no change in treatment become entirely free of symptoms. If the improvement coincides with the introduction of a new drug or diet, the favorable result may be ascribed to the new treatment instead of to the spontaneous remission characteristic of the disease. In many patients emotional factors seem to be all-important, and a change of jobs, a vacation or the settlement of family troubles, may produce complete relief of pain intractable to accepted methods of treatment. Finally, it must be remembered that ulcer symptoms are often relieved by any seriously and enthusiastically prescribed drug or method of therapy. There is much truth in the remark that all new cures for ulcer work well for a time.



Effect on Pain

The most impressive effect of tricyclamol is the prompt relief of pain. Illustrative of this point is the case of a 55-year-old man, with a long ulcer history, who could work only by eating frequently, taking large doses of antacids, atropine, and sedatives. On a convalescent ulcer diet and 50 mg. of tricyclamol 4 times a day, he felt, after one day, what he called "miraculous relief" of all distress. For the first time in years he was able to go through a day without gnawing pain. In some patients with severe pain, with tenderness and guarding of the epigastrium suggesting impending perforation, 20 mg. of tricyclamol intramuscularly often abolishes pain in a few minutes and the same amount intravenously produces almost immediate relief.

The relief of pain in peptic ulcer with tricyclamol is of interest, for it implies that a factor other than acidity may be a contributing cause of ulcer pain. Our experiments show that tricyclamol in therapeutic doses diminishes gastric acidity and decreases gastric peristalsis, with delay in emptying and slowing of intestinal motility. To determine whether the antisecretory or antispasmodic action of tricyclamol is

TABLE 3. Diagnoses and Duration and Results of Treatment with Tricyclamol in 105 Cases of Peptic Ulcer

Duration of treatment (mo.)	No. patients	Diagnosis	Results: X-ray disappearance of crater	Good	Fair	Poor
20	10	9 D.U. 1 G.U.	8 D.U. 1 G.U.	9		1 D.U. patient asymptomatic; crater larger
16	9	8 D.U. 1 G.U.	7 D.U. 1 G.U.	8		1 D.U. patient asymptomatic; crater unchanged
12–15	14	12 D.U. 2 marginal	7 D.U. 2 marginal	9	5	..
8–12	14	12 D.U. 2 G.U.	8 D.U. 2 G.U.	10	4	..
6–8	8	8 D.U.	5 D.U.	5	1	1 D.U. intractable pain; operation. perforation pancreas 1 D.U. hemorrhage; operation
3–6	28	25 D.U. 2 G.U. 1 duodenitis	9 D.U. 2 G.U. Duodenitis unchanged	18	9	1 D.U. hemorrhage when asymptomatic
1–3	19	19 D.U.	7 D.U.	17	2	..
Less than 1	3	3 D.U.	..	..	..	Discontinued treatment—no result
TOTALS	105	96 D.U. 6 G.U. 2 marginal 1 duodenitis	52 D.U. 6 G.U. 2 marginal	76	21	5

responsible for the relief of pain, we performed the following experiment: in 10 patients who were having spontaneous pain, after aspirating the gastric contents, we introduced 200 cc. or more of 0.5% hydrochloric acid into the stomach and reproduced characteristic ulcer pain. In 3 other patients with duodenal ulcer who were having spontaneous pain but who had been under treatment for 3–7 days, we were unable to produce pain. In those cases in which pain was produced it was promptly and completely abolished by intravenous injection of 20 mg. of tricyclamol. Efforts to reproduce the pain by introducing more acid into the stomach were unsuccessful. The following is a protocol of one of our experiments in a 60-year-old patient with a duodenal ulcer of 24 years' duration who was having spontaneous pain:

8:30 a.m.	Mild epigastric pain. Levin tube introduced; stomach aspirated, 75 cc. (pH 2.0)	10:15 a.m.	20 mg. tricyclamol intravenously
		10:18 a.m.	Pain greatly decreased
9:00 a.m.	Pain gone	10:20 a.m.	Pain gone
9:05 a.m.	200 cc. 0.5% HCl introduced into stomach	10:45 a.m.	No pain
		11:15 a.m.	200 cc. 0.5% HCl introduced into stomach
9:15 a.m.	Slight epigastric pain	11:30 a.m.	No pain
9:30 a.m.	200 cc. 0.5% HCl introduced into stomach	12:00 noon	No pain
		12:30 p.m.	No pain. Stomach aspirated (pH 2.0)
9:45 a.m.	Gradually increasing typical ulcer pain		
10:00 a.m.	Severe pain. Sample withdrawn (pH 1.2)		

Role of Motility

The question of pain in peptic ulcer is highly controversial and we do not mean to imply that our results establish the cause. The relief of pain in our cases could have been due to (1) the marked diminution of gastric peristalsis which prevents the acid from leaving the stomach and coming into contact with the ulcer, or (2) the cessation of abnormal activity of the stomach and duodenum. Our motility studies show that in patients with duodenal ulcer who have received 100 mg. of tricyclamol orally, an appreciable amount of gastric content enters the duodenum in 30 minutes. Since pain did not recur in any of our subjects within two hours in spite of the large amount of acid present in the stomach, some of which must have entered the duodenum, our experiments would seem to indicate that spasm or abnormal activity of the stomach or duodenum, rather than the presence of acid, may be the cause of duodenal ulcer pain. Doubt may be cast upon these conclusions since in these experiments the pH of the gastric juice in contact with the ulcer is unknown. Recent studies by Woodward and Schapiro[9] would indicate that when 0.10N HCl is inserted directly into the area of the ulcer, pain is produced which does not respond to adequate doses of Pro-Banthine.

Effect on Healing

In evaluating the effectiveness of any treatment of peptic ulcer, valuable evidence of cure is furnished by the disappearance of the

crater in cases in which a crater was previously demonstrated. When the ulcer crater cannot be demonstrated reliance must be placed upon observation of changes toward normality in the characteristically deformed bulb. If, on treatment, the patient becomes asymptomatic and the bulb loses its deformity, one has a fairly good indication of healing. In many cases, however, the bulb is so deformed that even when a clinical cure results the bulb may show little change in form. Furthermore, since a deformed bulb may result from spasm as well as from cicatricial contraction, and rarely from inflammation of contiguous organs, changes in degree of deformity may be misleading.

In the 105 patients treated with tricyclamol, craters disappeared in all 6 patients with gastric ulcers and 52 of the 75 patients with duodenal ulcers who were reexamined. Exact figures on rate of healing of chronic gastric and duodenal ulcers are hard to obtain. The reason for this is the difficulty and expense of repeated roentgen studies and the understandable reluctance of overburdened radiologists to do reexaminations, which, in most cases, at best supply data of academic interest only.

In this study we have not attempted to compare the rate of healing of ulcers treated with tricyclamol against those treated with other drugs. It is our clinical impression, however, that in many cases the addition of tricyclamol to the usual dietary and antacid regimen has caused large ulcers to heal relatively rapidly.

Side Effects

Our study indicates that tricyclamol, in the dosage used, has singularly few troublesome side effects. In only 1 of the 105 patients was the drug discontinued because of intolerable dryness of the mouth. In another patient the dose had to be cut in half for the same reason. Fifty-eight patients reported some dryness of the mouth which usually passed unnoticed after a week or so. In 4 cases constipation was a problem. One patient refused to take tricyclamol because of severe constipation. The other cases responded readily to magnesium oxide and it was unnecessary to change the dosage of the drug. In 1 case blurring of vision was extremely troublesome and the patient could not be persuaded to continue taking tricyclamol. In therapeutic doses tricyclamol has had no effect on urination. Although 18 of the patients were over 60 years of age no cases of urinary suppression were seen. Two patients with benign prostatic hypertrophy received as much as

30 mg. tricyclamol intravenously without production of urinary difficulty. There were no instances of tachycardia, abdominal distention, dermatitis, or stomatitis. An interesting and desirable side effect is a feeling of relaxation and tranquillity reported by 10 patients.

The development of side effects during anticholinergic therapy deserves further comment. Since peptic ulcer is accompanied by so much pain, distress, and disability, it seems illogical, when using such potent and useful drugs as the anticholinergics, to place too much stress upon side effects which are in most cases merely troublesome. A slight dryness of the mouth, for instance, is a small price to pay for relief of the severe pain so often experienced with a peptic ulcer. As a matter of fact, the only convenient evidence a physician has that anticholinergic effects are being produced from medication is the presence of some side effect such as dryness of the mouth. In our opinion, a frank discussion with the patient as to the effects we are trying to produce in order to further the healing of his ulcer usually results in acceptance of minor discomforts. A patient who is unwilling to tolerate a slight dryness of the mouth with concomitant relief of pain can hardly be having much distress.

Acquired Tolerance

No evidence of acquired tolerance was seen in any patient, even in those taking tricyclamol for 20 months. It was noted on numerous occasions that patients who had dryness of the mouth had the same degree of dryness with approximately equal doses in the later as in the earlier stages of treatment.

DISCUSSION

While the antisecretory effects of anticholinergic drugs are of great importance in the treatment of peptic ulcer, we believe that a major part of the therapeutic usefulness of trycyclamol is its antispasmodic action. The secretion of hydrochloric acid was decreased in 8 to 10 cases; motility was diminished in every one of the 10 cases. The antispasmodic action appears to be quite consistent. It is this effect, we believe, which produces the prompt relief of pain and which simplifies the management of peptic ulcer.

Cause of Ulcer Pain

The subject of ulcer pain has been the source of much controversy ever since Bonniger[10] 47 years ago demonstrated that the introduc-

tion of acid into the stomach of a patient with ulcer produced pain. The subsequent investigations of Palmer[11] and Bonney and Pickering[12] apparently established the preponderant part played by acid. Indeed, it is a matter of common, everyday experience that the administration of alkalis is a most efficient means of relieving ulcer pain and distress.

In recent years the introduction of many new anticholinergics has thrown doubt upon the acid theory. In patients with duodenal ulcer abnormal antral contractions have been shown to be related to pain.[13] Ruffin[14] demonstrated that the presence of acid within the ulcer crater played a minor role in pain production and that a disordered motility was the essential factor necessary for pain to occur. Our experiments have shown that in the presence of sufficient acid in the stomach to produce pain, tricyclamol intravenously can abolish pain for prolonged periods. Since tricyclamol could not have reduced the artificially produced hyperacidity to the point where the pain disappeared, it would seem that the effect was produced by causing a cessation of abnormal motility.

We cannot conclude that this is true in all ulcer patients because we have not studied a sufficient number of patients with gastric ulcer. As far as duodenal ulcers are concerned, our results tend to support Ruffin's observations that ". . . abnormal motor activity is the fundamental mechanism through which pain is produced."

Decreased Need for Antacids

In other respects, also, the use of tricyclamol in our series of patients has been encouraging. Recovery seems to be facilitated by the fast relief of distress and patients can tolerate more nutritious diets. We do not wish to imply that tricyclamol is a cure for peptic ulcer. We agree with Kirsner[15] that, ". . . accurate evaluation of therapy in peptic ulcer requires careful observation for prolonged periods, perhaps two to five years in relation to at least four criteria: relief of symptoms, rate of healing, incidence of complications and rate of recurrence." The results we obtained indicate, however, that tricyclamol, because of its antisecretory as well as its antispasmodic action, is a valuable adjunct in the treatment of peptic ulcer. The use of tricyclamol need not be limited to the treatment of peptic ulcer of any special type or severity. It has been demonstrated[16] that with a diet of hourly milk and cream, 4 Gm. of calcium carbonate is required every hour in order to reduce the acidity below the "proteolytic neutraliza-

tion point" of Hollander, or a pH of 5.0. When atropine, 1 mg. 4 times a day, is added to the above regimen, the amount of antacid necessary to produce the same degree of neutralization can be cut by two thirds. Since many antacids often cause severe constipation this ability of an anticholinergic drug to decrease the need of antacids is of appreciable clinical importance. Although this work was done with atropine the conclusions are probably valid for tricyclamol and other anticholinergics.[17]

Even though the antisecretory effects of anticholinergics are not predictable or constant in every case, we believe that inhibition of hydrochloric acid occurs often enough to make their use desirable in every case. It is obviously desirable to reduce the acid concentration of gastric juice for the very presence of an ulcer indicates that the organ cannot withstand the amount of acid present.

Continuing Observation

Patients should be told, however, that relief of pain does not mean cure or necessarily improvement in the ulcer. In some cases, even though the patient taking tricyclamol adheres rigidly to a dietary and antacid regimen, the ulcer may not improve and, indeed, may even hemorrhage as in 2 of our patients. Therefore, a patient who has become clinically well still requires careful observation and periodic reexamination.

Contraindications and Cautions

Tricyclamol, like other anticholinergics, should not be administered in glaucoma and with caution, if at all, in cardiospasm, prostatic hypertrophy and organic pyloric obstruction. In cases of gastric retention due to spasm the drug may be of benefit because its antisecretory effect may promote healing. This effect is somewhat counterbalanced, however, by the antispasmodic action which retards emptying. In cases of active hemorrhage, especially when surgery is a possibility, tricyclamol is contraindicated because of its tendency to cause gastric atony.

SUMMARY and CONCLUSIONS

1. In patients with peptic ulcer tricyclamol in therapeutic doses decreases the acid concentration of both fasting gastric juice and that following stimulation by alcohol. It has no effect on acidity of gastric juice secreted in response to insulin-induced hypoglycemia. Tricy-

clamol also diminishes the motility of the stomach and small intestine.

2. Tricyclamol was used in therapy of 104 patients with various types of ulcer and 1 patient with duodenitis. In 76 patients good symptomatic relief was obtained, and in 21 there was fair symptomatic relief. In 5 patients the results were poor. Three patients used the drug for too short a time to warrant a conclusion.

3. The optimum oral dose of tricyclamol is 50 mg. 4 times a day.

4. The most impressive therapeutic effect of tricyclamol is the prompt relief of pain.

5. Our studies indicate that pain in duodenal ulcer is probably caused by disordered motility rather than by hydrochloric acid.

6. Tricyclamol is a valuable agent in the treatment of peptic ulcer. It is not a cure for peptic ulcer and finds its greatest usefulness when combined with dietary and other conventional measures.

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CASE REPORTS

Volvulus of the Splenic Flexure

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VOLVULUS OF THE SPLENIC FLEXURE is an unusual type of large-bowel obstruction. To date, 1 operative case has been reported in the literature.[1] It is our purpose to add 2 more proved cases and to discuss their etiology.

ANATOMY

The peritoneal attachments[2] of the colon are fairly constant. Usually the cecum is completely encircled by peritoneum and enjoys good mobility. The ascending colon has variable reflections. A common or short mesentery may be present or none at all. The hepatic flexure is put in contact with the posterior wall of the abdomen by the peritoneum, which covers it anteriorly and laterally. Occasionally, envelopment is complete and a short mesocolon results. However, mobility is hindered by the liver. An extensive mesocolon surrounds the transverse colon, allowing for ample mobility and redundancy; however, fixation of its ends at the widely separated flexures is a formidable deterrent to volvulus. The splenic flexure is firmly attached by peritoneal folds, the phrenicocolic ligament, to the diaphragm opposite the left tenth and eleventh ribs. Its position varies. A long mesocolon fixes the sigmoid colon at two close anatomic points, the iliac colon and at the junction with the rectum. Thus, anatomic conditions predispose to redundancy and twisting.

Buenger[1] reported 2 cases of volvulus of the splenic flexure. One case, confirmed operatively, was caused by a thick adhesive band in the region of the transverse colon and left lateral abdominal wall. It caused incarceration, volvulus, and complete obstruction of the splenic flexure. The second case demonstrated a twist in the region of the splenic flexure on x-ray. Symptoms were transient, perhaps physiologic, due to the redundancy of both transverse and descending

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colon in proximity to the flexure. As such, it is probably not a bona fide volvulus.

Our 2 proved cases of volvulus of the splenic flexure are reported below.

CASE 1

W. W., a 63-year-old Negro male, was admitted to Bellevue Hospital on August 10, 1955, with the complaints of right chest pain and abdominal distention of 6 days' duration.

The chest pain, accompanied by a dry, nonproductive cough, persisted from onset until admission. Abdominal swelling became progressively worse. The day before entry, a bowel movement afforded some relief, but after that time neither feces nor flatus was passed. Abdominal discomfort, not crampy pain, was present without vomiting.

Past History

Past history revealed many similar episodes of distention in recent years which resolved spontaneously except for one bout early in 1954 that necessitated exploratory laparotomy, at which operative findings were negative. The patient was a known alcoholic and had been treated at another hospital for Laennec's cirrhosis. In addition, he had undergone treatment for active pulmonary tuberculosis. In recent months, signs and symptoms of congestive heart failure were controlled by digitalis.

Physical Findings

Chest. Dullness to percussion, bronchophony, bronchovesicular breath sounds, and coarse rales over the right lower chest inferiorly.

Abdomen and rectum. A greatly distended abdomen with a tympanitic percussion note over the upper half. Few low-pitched bowel sounds were heard. Bilateral, small, reducible inguinal hernias were present and a long, vertical scar with a small inferiorly situated horizontal component was noted in the left lower quadrant. Rectal examination was negative.

Radiologic Findings

Scout films of the abdomen revealed marked distention of the upper descending colon and splenic flexure with fluid levels at the latter site in the erect position. In addition, the transverse and right side of the colon were moderately dilated with gas and fecal material (Fig. 1).

Sigmoidoscopy to 10″ was negative; however, during manipulation, a considerable amount of flatus and some liquid feces were expelled from above. Subsequent scout films showed lessened distention of the splenic flexure. Barium enema filled the colon to the ileum. Considerable redundancy and a

twist of the splenic flexure was demonstrated (Fig. 2). Obstruction was relieved, and the diagnosis of intermittent volvulus was made.

Treatment and Surgical Findings

During the following 2 weeks abdominal distention waxed and waned. Relief was afforded by proctoscopy and insertion of a long tube to the flexure. The right-lower-lobe pneumonia responded to penicillin. On August 26, 1955, an elective exploratory laparotomy was done. The significant findings were volvulus of the splenic flexure with dilatation and thinning of the bowel wall; agenesis of the gastrocolic ligament (greater omentum) and lateral peritoneal-colic attachments. A partial colectomy with end-to-end anastomosis was done.

Recovery was uneventful except for one brief postoperative episode of hypotension. Barium enema before discharge from the hospital revealed a well-functioning anastomosis with proximal dilatation.

Pathology Report

"Specimen received consisted of colon from beyond the cecum to the sigmoid. It is dilated and thinned out and in its largest diameter measures 12 cm. There are no circumferential peritoneal attachments. The blood vessels enter on the concave side and are the sole attachment of the segment of colon. Microscopic sections showed no abnormalities."

CASE 2

E.K., a 70-year-old white male, was admitted to Bellevue Hospital on July 29, 1955, with the complaints of inability to move his bowels or pass flatus for 8 days, right lower quadrant colicky pain of 2 days' duration, and nausea for 1 day.

Past History

Past history revealed a nephrectomy in 1935, a right inguinal herniorraphy in 1940, and hospitalization for pneumonia and chronic heart failure in March, 1955. Since that time he had been maintained on Mercuhydrin and a salt-free diet and was asymptomatic except for chronic constipation.

Physical and Radiologic Findings

The pertinent physical findings on admission were a soft abdomen with a large cystic mass in the left upper quadrant. The mass was resonant to percussion, a finding suggestive of a locally distended bowel.

Proctoscopy was performed and a large amount of flatus together with some liquid stool was released. For 2 days the patient was treated conservatively with rectal and Levin tube drainage with minimal improvement.

Upper gastrointestinal series and small-bowel study done during March,

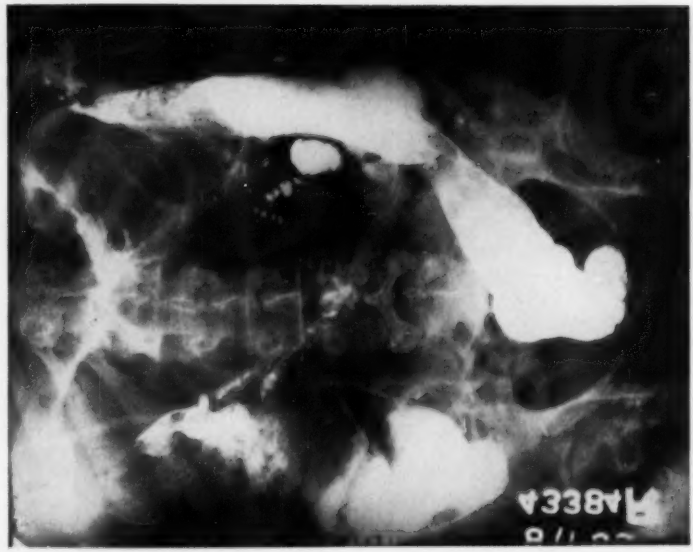

Fig. 2. Case 1. Barium enema reveals beaking of the proximal descending colon with marked dilatation of the splenic flexure and distal transverse colon.

Fig. 1. Case 1. Marked distention of the proximal descending colon and splenic flexure; lesser distention of the transverse and right colon.

Fig. 4. Case 2. Small-bowel series, 2-hour film, reveals a closed-loop obstruction at the splenic, flexure.

Fig. 3. Case 2. Upper gastrointestinal series, right lateral position, reveals a closed-loop obstruction at the splenic flexure.

Fig. 5. **Case 2. Barium enema shows narrowing of midsigmoid with dilatation and twist of the splenic flexure.**

1955, had revealed a volvulus of the splenic flexure (Figs. 3 and 4). Barium enema revealed a tubelike narrowing and "beaking" in the sigmoid, with shortening, and a straight descending colon (Fig. 5).

On July 31, 1955, an exploratory abdominal laparotomy was performed. In the midsigmoid the surgeon palpated an area of inflammatory thickening with marked narrowing of the lumen. Above this point the sigmoid and descending colon were straight and of normal diameter. The splenic flexure was markedly dilated and twisted, indicative of volvulus. A hemicolectomy and end-to-end anastomosis was performed. The surgical specimen measured 60 cm. in length and 40 cm. in circumference at its widest portion in the splenic flexure.

Pathology Report

"Sections through the area of narrowing in the sigmoid revealed many nerve cells between the longitudinal and transverse muscular coats. There is

hypertrophy of the muscular coats. There is a marked inflammatory process involving the mucosa."

DISCUSSION

In the first case, a very rare congenital absence of the greater omentum and peritoneal attachments at the flexures predisposed to volvulus of the splenic flexure. In the second case, a short mesocolon at the splenic flexure together with a chronic, benign obstruction in the sigmoid below allowed for progressive dilatation of the splenic flexure and twist. A splenic flexure with normal peritoneal attachments in the absence of distal pathology would not usually undergo volvulus. The more common site of a twist would be the sigmoid where redundancy and a long mesocolon with close attachments are normal occurrences.

SUMMARY

Two proved cases of volvulus of the splenic flexure the second and third to be reported in the literature, are described, and the associated congenital and acquired colonic disease are discussed.

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MEDICAL GRAND ROUNDS

E. Clinton Texter, M. D., and Hugo C. Moeller, M. D., *editors*

Report of a weekly Medical Grand Round held at the VA Research Hospital, edited by Hugo C. Moeller, M. D., and E. Clinton Texter, M. D. These rounds are conducted by Craig Borden, M.D., Chief of Medicine and presented by members of the staff of the VA Research Hospital. They are participated in jointly by the faculty and clinical clerks of Northwestern University Medical School and guests.

Postgastrectomy Syndromes

If it weren't for dumping, I would say we have a satisfactory operation for ulcer.
—OWEN WANGENSTEEN (1953)

Dr. Craig Borden: This morning's conference will be devoted to a discussion of the complications of gastric surgery. Dr. Wennemark will present the case.

CASE REPORT

Dr. James Wennemark: F. G. (5218-3158), a 46-year-old white married male claims adjuster, was admitted to the Research Hospital on June 29, 1955, with complaints of diarrhea and weight loss.

Medical History

In 1946, an upper gastrointestinal x-ray revealed an active duodenal ulcer. His past history included repeated bouts of vomiting and 3 episodes of hemorrhage, none requiring blood transfusions. He entered Hines Hospital in July, 1953, with a history of vomiting for 5 days. X-rays revealed "a deformity of the duodenal ulcer with a pseudo diverticulum compatible with residual of old ulcer pathology; no evidence of obstruction." The symptoms disappeared soon after he was placed on strict ulcer management. On August 6, 1953, a subtotal gastric resection with a Billroth I anastomosis was performed. The patient had an uneventful postoperative course and was discharged on August 18, 1953.

The patient continued to gain weight after discharge and was relatively well. After approximately two months, he noticed progressive anorexia, with occasional vomiting. The vomiting increased, and there was subsequent weight

loss of 36 pounds. There was no associated pain, fever, or jaundice. He was readmitted to Hines Hospital on November 18, 1953. Laboratory examination at that time revealed total protein of 5.8 Gm./100 cc. (albumin 4.0 Gm., globulin 1.8 Gm.) and a hemoglobin of 13 Gm./100 cc. Upper gastrointestinal x-ray demonstrated a well-functioning gastric stoma.

The patient returned to work but continued to lose weight. In December, 1954, he developed diarrhea with abdominal cramps, the stools numbering 3–14 per day and varying from loose and formed to watery. He developed flushing, weakness, faintness, and sweating shortly after eating. On December 31, 1954, he underwent a hemorrhoidectomy, without relief of symptoms. The diarrhea and cramps continued until admission to this hospital.

Psychiatric History

Psychiatric history showed that the patient had a depression in mood which at times had been so severe as to provoke fantasies of self-destruction. He dated his loss of interest in living to around 1945–46, when his father, mother, and brother died within a period of 15 months. On receiving news of the death of his brother the patient became depressed and considered suicide.

Fig. 1. **X-ray showing resected stomach with normally functioning stoma.**

Although he had a long history of ulcer distress, the symptoms disappeared while he was in the Army.

A few weeks after discharge, in January, 1954, the symptoms recurred. It was the impression of the psychiatric consultant that the nausea, vomiting, and aversion to food were manifestations of a psychogenic gastrointestinal reaction.

Physical Findings

Physical examination on admission revealed the patient to be severely emaciated, weighing 89 pounds. Positive physical findings included a liver palpable 3 fingerbreadths below the right costal margin, increased bowel sounds, and bilateral pitting edema. There was some weakness of both legs, with decreased position and vibratory sense of both lower legs. There was slight diminution in the perception of touch and pain below the knees bilaterally. The neurologist felt that these neuropathic changes were due to malnutrition.

Laboratory Findings

Pertinent laboratory data on admission included: hemoglobin 10.2 Gm./100 cc.; WBC 2800/cu. mm.; total protein 3.4 Gm./100 cc. (albumin 2.5 Gm. and globulin 0.9 Gm.). Alkaline phosphatase was 6.4 Bodansky units; serum

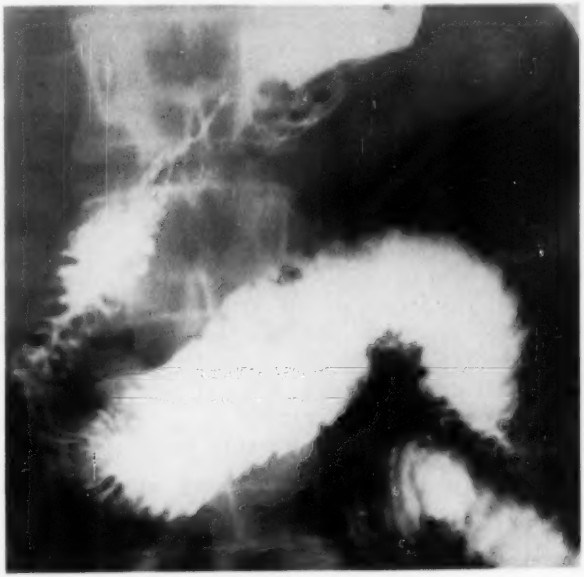

Fig. 2. **X-ray showing dilated loop of small bowel.**

bilirubin 2.6 mg./100 cc. total, 1.7 mg./100 cc. direct; cephalin flocculation 1 plus; thymol turbidity 5 units; bromsulfalein retention after 45 minutes, 12.2 per cent; calcium 4.7 mEq.; and prothrombin time 88 per cent. A glucose tolerance curve revealed fasting sugar, 79 mg./100 cc.; ½ hour 200 mg./100 cc.; 1 hour 280 mg./100 cc.; 2 hours 116 mg./100 cc.; 3 hours 69.6 mg./100 cc.; 4 hours 72.5 mg./100 cc. Stool examinations were negative for ova, parasites and occult blood. Quantitative analysis of stool fat showed a total fat of 11.6 per cent. Histamine test revealed 4 degrees total acidity. Proctoscopy was negative. Dr. Cailleteau will show the x-ray.

X-ray

Dr. Giles Cailleteau: Upper gastrointestinal x-ray showed the small gastric stump secondary to earlier surgery (Fig. 1). There was rapid passage of barium through this region with moderate dilation of the small bowel (Fig. 2). Flat plate of the abdomen did not reveal any calcification in the pancreas.

Therapy

Dr. Wennemark: There was a good response to a moderately low fat diet, consisting of six equal feedings; atropine $\frac{1}{100}$ gr. 4 times a day; pancreatin 30 gr. 3 times a day; and phenobarbital ¼ gr. 4 times a day; The patient was instructed to lie down for 1 hour after eating. The stools decreased to 1 or 2 per day; the peripheral neuritis was markedly improved.

Course After Discharge

The patient was discharged on October 4, 1955, weighing 105 pounds without edema. The total serum protein on discharge was 5.56 Gm./100 cc. (albumin 3.88 Gm., globulin 1.68 Gm.). He continued to gain weight and was able to return to work. When last seen at Northwestern University Medical Clinic on October 26, 1955, he reported that his appetite was good; stools were normal in consistency, and that he felt generally well. We have subsequently heard that he committed suicide.

Dr. Borden: Do you want to comment on the case, Dr. Texter?

Dr. Clinton Texter: The patient showed typical manifestations of several of the postgastrectomy syndromes. He had the dumping syndrome which may follow gastrectomy. He also had postgastrectomy diarrhea, with increased loss of fat in the stools and he had a nutritional disturbance which was, at least in part, associated with surgery.

Dr. Borden: Dr. Wennemark will now present a discussion of this syndrome.

REVIEW OF POSTGASTRECTOMY SYNDROME

Development of Gastric Surgery

Dr. Wennemark: Although Pean performed the first partial gastrectomy in 1879, the name of Billroth is associated with the early development of gastric

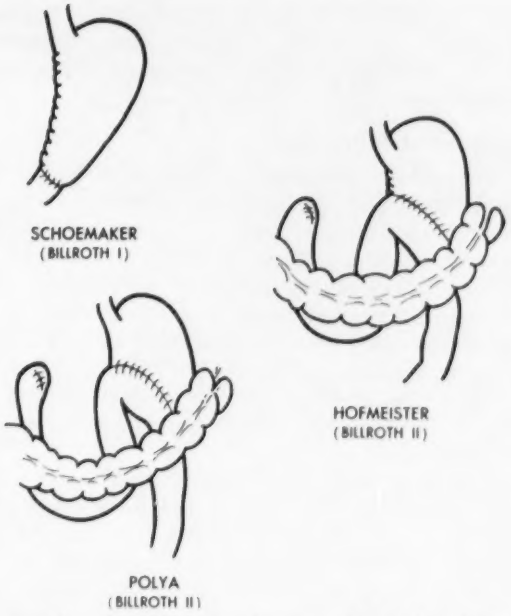

Fig. 3. **Diagrammatic representation of commonly employed types of gastric resection (From Barborka, C. J., and Texter, E. C., Jr.: *Peptic Ulcer: Diagnosis and Treatment.* Reprinted courtesy Little, Brown and Company)**

surgery. In 1881, Billroth performed a pyloric resection and gastroduodenal anastomosis which became known as the Billroth I type of resection. About four years later he modified the type of anastomosis from a gastroduodenal to a gastrojejunal; this procedure has been termed the Billroth II operation (Fig. 3). Since that time, there have been a multitude of variations and modifications of this procedure, each of them carrying the name of its originator, and each supposedly endowed with some advantage.

It would appear from the clinical and experimental evidence that there is an advantage in performing the Billroth I operation. The incidence of the early postprandial syndrome is somewhat less and there is also a decrease in the absorptive problems manifested by steatorrhea and nitrogen loss.[1] However, the technical aspects of the surgical approach must be individualized not only to the particular patient but also to the preference of the surgeon performing the operation.

Symptoms

Both surgeons and internists are becoming increasingly aware of unfavorable sequelae which may occur following partial gastrectomy.

The postgastrectomy syndrome can be divided into the symptoms occurring in the early postprandial period, or the so-called "dumping" syndrome suggested by Mix[2] in 1922, and those occurring later, known as the late postprandial symptoms.

Early Postprandial Syndrome

The early postprandial symptoms in order of frequency are epigastric fullness, nausea, vomiting of bile, belching, explosive diarrhea, borborygmi, and vomiting of food. The vasomotor component includes an unpleasant feeling of warmth, weakness, dizziness, pallor, palpitations, perspiration, chilliness, tachycardia, drowsiness, and loss of consciousness. The symptoms may come on immediately after eating, and are alleviated by lying down. Muir[3] believes that anything occurring later than one-half hour is not really part of the dumping syndrome, while others[4, 5] feel it may come on as late as 1 hour after meals. The symptoms may last from 20 minutes to 2½ hours, with an average of about one hour. Large meals of high carbohydrate content aggravate the condition.

Anemia, increased loss of fat and nitrogen in the stools, and inability to maintain body weight may result from continuance of symptoms.

Incidence. The great variation in incidence in the literature supports the contention that there is a difference of interpretation of the symptoms and the criteria for the diagnosis is not firmly established. However, it is generally accepted that the incidence of severe, incapacitating symptoms is 4–10 per cent.[6, 7] The incidence of moderate distress without nausea and vomiting is probably somewhere between 20 and 40 per cent. The incidence of symptoms following the Billroth I appears to be lower than the Billroth II operation.[8, 9, 10]

Etiology. The following etiologic factors have been proposed as important in the pathogenesis of this condition:

1. Distention of the jejunum due to rapid emptying of the gastric remnant and overflooding of the jejunum.
2. Stretching of the gastric remnant.
3. Coincident hyperglycemia due to rapid absorption from the upper small intestine.
4. Reflux of food into the afferent loop and distention of this segment.
5. Gastritis and jejunitis.
6. Tension on the gastroesophageal junction caused by the weight of the meal.
7. Kinking of the afferent loop and hyperperistalsis.
8. Absorption of toxic materials.
9. Anacidity.
10. Reflex action of the adrenal glands due to irritation of the mucosal wall.
11. A strong psychic stimulus.

Some of the above hypotheses have been tested experimentally with varying results. Adlersberg and Hammerschlag[4, 11] studied 13 patients with a Billroth II resection and 1 with a total gastrectomy and found all to have a rapid emptying of the gastric remnant with a slight distention of the upper jejunal loop coincidental with the symptoms. Butler and Capper[10] found that the stomal emptying time was about 40 minutes with a Billroth II resection, but that the stomal descent was 2 cm. in the nonsymptomatic cases in comparison to the 7 cm. in the symptomatic cases. In patients with a Billroth I resection, the average emptying time was 1 hour in 90 per cent of the cases and the descent of the stoma was 1.5 cm. Stretching of the gastric remnant may be a contributory etiologic factor.

Since an abnormal oral-glucose-tolerance curve is frequently observed in postgastrectomy patients, some[12] have related symptoms of the dumping syndrome to hyperglycemia. This concept has not been substantiated by other workers.[13, 14] Fisher *et al.*[7] state that they can reproduce symptoms in 90 per cent of gastrectomy patients with 150 cc. of 50 per cent glucose instilled in the jejunum when the symptoms exist clinically, and that the symptoms can be induced in normal people by the same method. The effect of the introduction of the hypertonic solution into the jejunum with the subsequent increase in volume due to osmotic pressure is an important etiologic factor.

The effect of distention of the afferent loop has been studied by the inflation of balloons. This procedure induced symptoms in patients with the clinical entity. Butler[10] produced symptoms in patients by introducing a bag of mercury equivalent to the weight of the meal. He concluded that the epigastric symptoms are due to the distention of the jejunum and the vasomotor symptoms are due to the weight of the meal on the cardioesophageal junction.

Late Postprandial Syndrome

The term "late postprandial gastrectomy syndrome" has been applied to the symptoms—dizziness, palpitations, headache, perspiration, and occasionally unconsciousness, without severe gastrointestinal complaints—which occur from 2 to 3 hours after eating.

Incidence. The incidence of this complication is much less frequent than the early postprandial gastrectomy syndrome, varying from 3 to 10 per cent according to various authors.[3, 15, 16]

Etiologic Significance of Glucose Level. There is a good correlation of these symptoms with low blood-glucose level. Various theories have been suggested to account for the hypoglycemia including the following:

1. Rapid jejunal filling → rapid absorption of glucose → hyperglycemia → oversecretion of the pancreas. The glucose in the jejunum is rapidly depleted and there is no glucose to cover the increased insulin secretion.
2. Dysfunction of the autonomic nervous system.
3. Disturbed glucoregulatory mechanism of the liver.
4. Abnormal insulin sensitivity.

The typical glucose-tolerance curve shows a rapid rise in 15 minutes to ½ hour to hyperglycemia levels, frequently in the range of 250 mg./100 cc. Elevation remains fairly constant for 2–3 hours, when it falls off rapidly to hypoglycemic levels (20–60 mg./100 cc). In patients who show the clinical entity of the LPP syndrome, the symptoms can almost always be reproduced in the hypoglycemic phase of the glucose-tolerance curve. Physical exercise may be important in precipitating the late postprandial symptoms and it has been noted that the symptoms can usually be relieved by the feeding of a small amount of carbohydrate.

Nutritional Problems

Anemias

The anemia, weight loss, and disturbance in absorption which occurs after gastrectomy present a difficult problem in nutrition. It is rather rare for a megaloblastic anemia to occur following partial gastrectomy.[17] An iron-deficiency anemia following partial gastrectomy is very common. It is usually a hypochromic microcytic anemia and is more common in females before the menopausal age. A low serum iron is usually associated with the anemia, and some people believe that the rapid passage of the iron through the upper G.I. tract prevents its proper absorption.[18]

Weight

There has been considerable discussion concerning the weight status of postgastrectomy patients.[19] The maintenance of weight may be a particular problem. In addition there is the problem of dealing with the severely underweight individual who cannot gain weight postoperatively.[20] The problem usually becomes acute when a patient encounters absorptive difficulties with the subsequent steatorrhea and nitrogen loss, especially if the intake is already decreased because of severe postprandial symptoms.

Steatorrhea

The exact incidence of steatorrhea is difficult to determine. Everson,[21] in an excellent review of the literature, found impairment of fat absorption in a considerable number of patients. There appears to be less postoperative steatorrhea with the Billroth I operation, but some degree of steatorrhea appears to be the rule after the Billroth II operation.[1, 22]

Principles of Treatment

The postgastrectomy patient should be instructed to avoid both large intake at any one time and high-carbohydrate intakes. Anemia should be corrected by iron therapy or, in a refractory case, by liver extract. The mild cases of steatorrhea do not require any special therapy. Although the treatment of severe cases of malnutrition and steatorrhea is generally unsatis-

factory, small feedings administered 6 times a day may relieve the patient of the symptoms. Reduction of hypermotility by anticholinergic drugs may help. Pancreatin may be valuable in certain cases. Occasionally the changing of the gastrojejunal to a gastroduodenal anastomosis may be helpful.

GENERAL DISCUSSION

Dr. Borden: I know that several people would like to comment on this general subject of postgastrectomy syndrome. Do you want to open the discussion, Dr. Texter?

Dr. Texter: It is a common observation that dumping seems to be more common in the unstable individual, as illustrated by the patient today. There is a striking similarity between the vasomotor component of the dumping syndrome and the anxiety syndrome. Those of us who have been plagued by management of these problems feel that much of the frequency of the dumping syndrome, or the variation in frequency, depends upon the selection of cases preoperatively, and we are constantly annoying the surgeons by saying, "This patient is not a good surgical risk from the psychological standpoint."

The studies of Machella[23] should be mentioned. By inflation of balloons in the jejunum, he could reproduce exactly the symptoms of dumping. Distention of the jejunum appears also to be a factor in the case reported. Some surgeons feel that dumping is less common with a smaller anastomosis, as in the Hofmeister procedure.

Dr. Frederick Preston: There are some recent studies done by groups in New York, at Memorial Hospital, and by Roberts *et al.*[24] and Wollaeger,[22] that show that the dumping syndrome is accompanied by a temporary decrease in blood volume. It can be produced experimentally in patients by introduction of a hypertonic solution into the stomach.

They feel that a decrease in blood volume and an increase in the amount of fluid in the jejunum, which may range from a few hundred cubic centimeters up to about a thousand or more, are the chief mechanisms responsible in the dumping syndrome.

Some of these new studies that have been presented here by Everson[1, 21] and Wollaeger[22] have made us think that probably the Billroth I operation is better than the Billroth II. We now use the Billroth I more than we did previously. However, it tends to be accompanied by a higher instance of recurrent ulcer. In the "old days," and I mean by that 20 years ago, the operation was a bit in disrepute. We have found that one can take out more stomach doing a Billroth I operation and still have a low incidence of recurrent ulcer.

Dr. Borden: Are there other comments from the audience? Dr. Wolf, would you care to comment about the psychologic aspect of the dumping syndrome?

Dr. Ernest Wolf: One of the things that does occur, which might be interesting

to mention, is that a small percentage of patients develop a paranoid psychosis after gastrectomy. It is hard to evaluate something like this because psychological disturbances that patients have postsurgically are frequently either not recognized or not diagnosed accurately. I wonder, for instance, why this particular patient that was mentioned today commited suicide? It seems that there may have been some relation to the surgery, but it is not specifically indicated. What it meant to him is not clear.

I know of a study in progress at present concerning the psychological changes that occur after mitral valvotomy. The reaction of the patient after this particular type of surgery depends more on the patient's personality rather than on the type of surgery that is being performed.

Dr. Robert Gilbert: There was another patient, some months back, Dr. Wolf, who committed suicide after a gastrectomy.

Dr. Borden: I don't think the type of surgery is specific, as Dr. Wolf mentioned, because there have been several suicides following mitral valvotomy. I don't think there is any difference in the incidence of the psychological complication following the two procedures.

Dr. Wolf: The psychological reaction will depend more on the patient's previous illness, and what the illness he had meant to him before the surgery, and what the surgery meant to him, rather than the kind of surgery it was.

Dr. Texter: I think that emphasizes the point I was trying to make—that unless you are careful in selecting these people, you let slip in the anxious people, and they are the ones more likely to develop the postoperative symptoms.

Dr. Wolf: It might be helpful to develop some criteria on that.

Dr. Hugo Moeller: I'd like to second Dr. Texter's crusade for careful psychologic evaluation of the ulcer patient before advising gastrectomy. The occurrence of the postgastrectomy syndrome is rare after resection for a malignancy. This suggests that the cancer patient may have a different psychologic approach to his problem than the patient with a gastric or duodenal ulcer.

Dr. Everett Shockett: Perhaps one should think not only of selecting the patient for surgery but also of selecting the operation. For instance, there are a lot of people, underweight and nervous, on whom you would never think of doing a resection, but would prefer a vagotomy and gastroenterostomy.

Dr. Borden: It seems to me that while there is a discrepancy in the literature relative to the incidence of serious steatorrhea, all of these patients have increased fat excretion in the stool, and the more carefully one does biochemical studies the more one can delineate a disability in the normal function of the gastrointestinal tract.

Dr. Moeller: I am impressed with the work of Butler,[10] in which he reproduced symptoms by the introduction of a bag of mercury equivalent to the weight of the meal. I wonder whether Dr. Preston has had any personal experience with the suspension operation and whether he has any comments on the success of this procedure.

Dr. Preston: The British people talk about that—the one way to correct the dumping syndrome is to suspend the stomach on the round ligament of the liver.

SUMMARY

Subtotal gastrectomy may be followed by a group of disturbances which include the early and late postprandial symptoms, anemia, increased fat and nitrogen loss, associated with a varying degree of weight loss and malnutrition. The theories of etiology and current concepts of treatment have been discussed.

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EDITORIAL

The Dumping Syndrome

WIDESPREAD ACCEPTANCE and practice of gastrectomy for the cure of complicated peptic ulcer admittedly has been followed by a number of undesirable side effects which have marred many of the otherwise acceptable clinical results. Interest in and publicity given to these postgastrectomy complaints seem to be out of proportion to their incidence and general importance, but like many other medical problems they are deeply significant to the individual patient who plays host to the problem.

SELECTION OF PATIENTS FOR SURGERY

In an effort to orient our thinking on these issues we should keep in mind the fact that good medical management should control at least 85 and perhaps as high as 90 per cent of all peptic ulcer patients. This means that of an original group of 1000 patients only from 100 to 150 will come to surgery. Perforation, hemorrhage, and obstruction with weight loss all are clear-cut complications and the logic of surgical intervention for each is usually a matter of unanimous agreement. The more variable indications will be found among those listed as "intractable," and here the subjective evaluation is more important and apt to be weighted by personal prejudice or interest. In this judgment the patient, the gastroenterologist, and the surgeon each contributes substantially to the decision for or against surgery.

When these surgical patients later are evaluated and the postgastrectomy group carefully studied, the incidence of disagreeable symptoms is found to vary to some extent with the surgical procedure utilized, the selected patient, and the clinician who tabulates the data. Under the most critical evaluation it may be concluded that about 30 per cent of these patients have merely substituted a new set of complaints for their old ones, with four or five individuals being completely incapacitated in the sense that they are economically unproductive. A more practical interpretation usually is that 90

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per cent of the patients are quite satisfied with their new situation; about 5 to 8 per cent have bothersome complaints, with two or three patients of the original 1000 being real "gastric cripples;" and 2 patients may be dead.

From this type of analysis one quickly can see that of the original 1000 patients with peptic ulcer, the combined efforts of the gastroenterologist and the surgeon are such that the disease seems to be rather well treated overall, there being only 10 to 30 patients out of the original group who persist with unsolved problems, and only 2 have died. Now, while this may sound like some sort of armchair idealism, how does this situation compare to treatment without surgery? The hospital study of Moore,[1] which admittedly includes many seriously ill patients, also points up the fact that if 1000 such patients either refuse or are refused surgical services during the course of treatment for peptic ulcer, one can expect at least 22 to die under medical management. How often it has been said, "Better to have a live patient with a complaint, than a dead one without it"!

Why do these patients complain after what should have been adequate surgery for their problems? In the first instance, the choice of patient is of the greatest importance. It should be appreciated that patients with extensive lesions at the time of operation tend to have less severe postcibal symptoms. The psychoneurotic with persistent symptoms of intractable ulcer, who at surgery presents little pathology, will never be cured by gastrectomy, and often will be harmed by it. While I might often be concerned during the course of a gastrectomy about the factors of delay which make my dissection at the time more tedious and difficult than it otherwise might be, nonetheless at the same time I cannot help commending my medical colleagues for their astuteness in their choice of patients for eventual surgery. If one were to use scar tissue as an assessment of medical delay our patients might often be catalogued as having been either neglected or "overtreated," but on the other hand their low incidence of the postgastrectomy syndrome is so pleasing that it is impossible to find fault with this type of medical advisor. On the other hand, the perceptive surgeon soon learns to recognize the hypersensitive individual with a multitude of gastrointestinal complaints. Such a patient needs many types of reassurance. In this situation his internist is much better qualified than the surgeon to handle his problem.

CAUSES OF DUMPING

In this regard it should be pointed out that the dumping syndrome rarely has been reported in people who have never had any gastrointestinal surgery with such conditions as gastrointestinal allergy, emotional hypersensitivity, and some types of enteritis. A patient whose only abnormality was an esophageal hiatus hernia has been reported as showing this syndrome.[2] These complaints seem to arise from a rapid outpouring of food through a patulous pylorus. A similar clinical response can be produced by means of running food too rapidly into a jejunostomy or by using food that is too cold or too concentrated.

The dumping or "efferent loop" syndrome has been reproduced by the inflation of a balloon in the jejunum, and this has been likened to the rapid entry of a large amount of recently ingested food from the gastric remnant to the jejunum.[3] Another interpretation, more physiologic and far more intriguing, is that of Roberts,[4] who shows a decreased blood volume coincident with the symptomatic period after eating. The passage of hypertonic material into the intestine followed by subsequent withdrawal of plasma and water from the mesenteric bed might well explain these symptoms.

SELECTION OF TYPE OF OPERATION

In either case, after we have carefully chosen our patient and have ascertained that pathology exists, we must tailor our operation to the problem at hand. The patulous Polya type of anastomosis following a 75 per cent resection with the efferent loop coming off the greater curvature obviously can duplicate the described mechanisms. Partially successful efforts to prevent this have been demonstrated in the Hofmeister modification, using a very small stoma.

Even though patient selection and physician-evaluation of postoperative results may be variables that seriously alter the validity of clinical conclusions from any series, there have emerged during the past decade certain observations that may further reduce the severity of these postsurgical problems. For benign gastric ulcer we still lean heavily upon resections, but they need not be so extreme. The Bilroth I type of anastomosis has increased in popularity because of the resultant improved postoperative nutritional status. While postoperative complaints still occur, they are less severe and largely disappear within a year. The inclusive nutritional studies of Zollinger[5, 6] will

serve indirectly to reduce the incidence of the "dumping" complaint by leading to better recognition of the fact that hemiresection coupled with vagotomy and a Bilroth I anastomosis is followed by satisfactory weight gain in many patients, moderate gain in others, and failure of weight gain only in rare instances. This latter procedure has been especially valuable in those duodenal ulcer patients who prior to their illness never had demonstrated previous ability to reach a satisfactory weight level, and who now have serious ulcer problems. More conservative and equally satisfactory with respect to a low rate of ulcer recurrence is the procedure used by Weinberg and Farris,[7] whose 500 patients have undergone complete vagotomy with a generous pyloroplasty. Ninety per cent of their patients have done well. Where recurrent symptoms have created the necessity for secondary resection, their plan incorporates the obvious distinct surgical advantage at the time of the second procedure of providing a clear operative field uncomplicated by previous gastroenterostomy.

If we are to eliminate the more serious objections to 75 per cent gastrectomy, we must alter slightly our attitude toward the surgical eradication of peptic ulcer.[8] We must eventually come to the agreement that the surgeon should not be a "one-operation man." He should not be a vagotomy enthusiast, nor devoted to the seven-eighths gastrectomy nor to the short circuit. Since we all agree that conservative care is the essence of good treatment for peptic ulcer, it is not inappropriate to select a definitive but conservative procedure for some patients when surgical intervention is indicated. Only too often does it happen that when the internist ultimately concludes that surgery for an intractable ulcer now is imperative, he admonishes the surgeon that the latter must now (and forever) eliminate all possible source of gastric acidity with one major operation. The occasional internist will take the attitude that the surgeon must, in three hours, do everything for the patient that fifteen years of medical management has failed to accomplish. If, over the course of years, one lone patient presents some disturbing postgastrectomy symptoms, the surgeon is immediately admonished that the operation has crippled this otherwise gainfully employed patient, and from this date hence no other patients of this particular internist are to be gastrectomized!

Since each patient presents an individual problem in applied gastric physiology, it would seem more logical to approach the pathology without a preconceived notion of what the operation should consist of. This not only will diminish the mortality where duodenal stump

closure is dangerous, but also will reduce greatly those postoperative dumping problems, which seem to be directly related to extensive gastrectomy. In the long run far fewer than 10 per cent of these selected patients would require secondary surgery if this practice were followed.

ALLEVIATION OF DUMPING

While this essentially is a forward-looking view, some mention should be made of methods of salvaging patients who have a current postgastrectomy problem. The interposition of jejunal loop as practiced by Henley[9] is worthy of comment. This procedure can be used either as a routine at the time of the gastrectomy, or later when it appears that the gastric pouch is too small to accommodate the daily nutritional requirements of a hard-working patient. This ingenious discovery has proven to be most helpful in rehabilitating the most severely ill "gastric cripples."

WALTER W. CARROLL, M.D.

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Pearls of Gastroenterology

Cardia and Diaphragm

EDITOR'S NOTE: The Journal is privileged to present these excerpts from a collection of capsules of gastroenterologic information compiled over the years by Dr. Eddy D. Palmer, Chief of Gastroenterology, Walter Reed Army Hospital, Washington, D. C. Dr. Palmer is a member of the Editorial Board of this Journal.

AUTHOR'S NOTE: This is a potpourri of favorite information about gastroenterology. It is strictly random information, some included because it is important, some because it may easily be overlooked during the reading of the detailed standard texts, and some because it may have special meaning for gastroenterology as it is practiced during this particular era.

The references which follow some of the statements do not, by any means, indicate the sources of the statements, but rather places to look for further information.—E.D.P.

Esophagogastric Junction

¶ The nature of the closing mechanism between the stomach and esophagus remains enigmatic. There is no anatomic sphincter here. The crura impinge to some degree on the esophagus when it is distended, but there appears to be no important extrinsic control over function at the cardia.

¶ Any part of the gastrointestinal tract which is lined with gastric mucosa continuous with that of the stomach proper must be considered stomach because it functions as stomach and because it falls heir to all of the diseases of the stomach. It has been found that part or most of the "abdominal esophagus" is actually stomach, that the normal stomach configuration includes a tubelike extension at the cardia, and that the esophagogastric mucosal junction normally undergoes rhythmic migration back and forth, with an excursion of 2 or 3 cm. Thus, the "abdominal esophagus" is created and obliterated from time to time. Thus, too, the gross configuration must be dissociated from definition of the stomach's limits. The regional living anatomy differs considerably from the dead anatomy (*Radiology 60:* 825, 1953).

¶ Cardia of the stomach directly overlies the medial border of the spleen.

¶ Transesophagoscopic fixation of silver brain clips to the esophagogastric junction provides a useful technic for studying the normal as well as the abnormal state of the esophagus and the junction (*Am. J. Roentgenol. 69:* 294, 1953).

¶ One of the thorniest of regional problems: the normal physiologic relationships between the cardia and the heart and coronary vessels.

BOOKS

Diseases of the Liver and Biliary System. SHEILA SHERLOCK, M.D. Springfield, Ill., Charles C Thomas, 1955.

Dr. Sheila Sherlock, by virtue of her rich experience and her significant contributions, is as qualified to write a book on the liver as anyone in contemporary medicine. "My aim in writing this book," she states, "has been to present a comprehensive and up-to-date account of diseases of the liver and biliary system, which I hope will be of value to physicians, surgeons, and pathologists and also a reference book for the clinical student." It does all these in a succinct and authoritative fashion. An amazing amount of material is presented in this relatively small book. The author avoids controversial matters for the most part, and states her point of view clearly. The bibliography is generous, selective, and useful. The first half of the book deals with the pathologic physiology of hepatic disease and the second half deals with clinical disease in more conventional style. The tables, charts, and summaries are helpful guides to the student and practitioner.

The only criticism this reviewer might offer concerns the form of presentation. Since the first part of the book deals with pathologic physiology and the latter portion with clinical application, there is need of frequent cross-references. At times this has the effect of interrupting the continuity of ideas or discussion.—ARTHUR J. PATEK, JR.

The Biliary Tract, with Special Reference to the Common Bile Duct. JULIAN A. STERLING, M.D. Baltimore, Md., Williams & Wilkins Company, 1955, 94 illus., 384 pp., $10.

This book essays to incorporate in a single volume all the essential information regarding the biliary tract and its disorders. The book is neatly arranged and fairly well illustrated, particularly the chapter dealing with radiologic aspects of biliary tract disease. Clinical manifestations, laboratory observations, and medical management of bile duct disease are discussed broadly and without

the usual subdivision into varieties of disorders affecting the bile ducts. The chapter on anatomy is especially good because it contains a résumé of the observations which the author has made and previously described on the morphology of the common duct and the choledochal sphincter. The style of writing is somewhat choppy and the text is broken into numerous small paragraphs. A bibliography is provided at the end of each chapter but no direct reference is made in the text to the works listed in the bibliography. A small separate chapter is devoted to lesions of the pancreas, nearly all of which, however, is concerned with pancreatitis. While it may be difficult to ignore the pancreas in a treatise concerned with the biliary tract, it is doubtful that a weighted chapter of such brevity is of great value.

The Biliary Tract will be of interest to physicians and surgeons who frequently have to deal with this system. It should be particularly attractive to any who are especially interested in the anatomy of the bile ducts and the choledochal sphincter area. It should also prove useful to those who may simply wish to find within one volume current information regarding the biliary tract and its disorders.—J. Edward Berk

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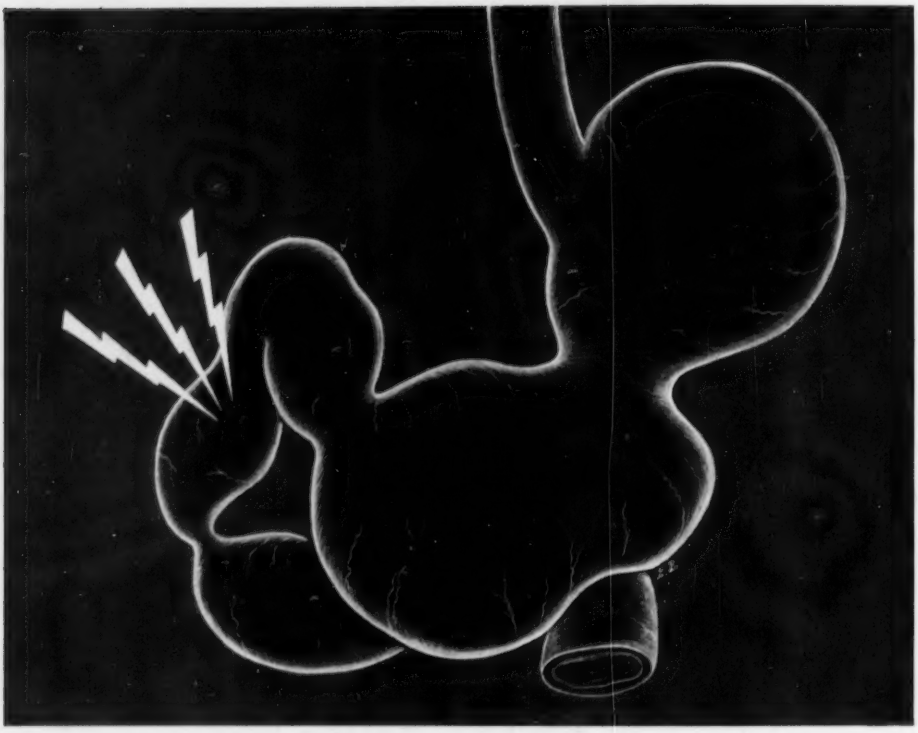

Abnormal Motility as the Cause of Ulcer Pain

Until recently the general opinion was held that ulcer pain was primarily caused by the presence of hydrochloric acid on the surface of the ulcer.

Present investigations[1,2] on the relationship of acidity and muscular activity to ulcer pain have led to the following concept of its etiologic factor:

> "... abnormal motility[2] is the fundamental mechanism through which ulcer pain is produced. For the production and perception of ulcer pain there must be, one, a stimulus, HCl or others less well understood; two, an intact motor nerve supply to the stomach and duodenum; three, altered gastro-duodenal motility; and four, an intact sensory pathway to the cerebral cortex."

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